A novel *de novo* SCN8A mutation in an Italian child treated with Levetiracetam: a case in discussion

Cecilia Galati
Adan Rodolfo Isgrò
Elisa Lo Re
Nunzia Calabrò
Domenica Lucia Sgro
Maria Spanò
Antonella Gagliano

Department of Human Pathology of the Adult and Developmental Age "Gaetano Barresi", Unit of Child Neurology and Psychiatry, University of Messina, Messina, Italy

Corresponding author:
Cecilia Galati
Department of Human Pathology of the Adult and Developmental Age "Gaetano Barresi", Unit of Child
Neurology and Psychiatry, University of Messina, Messina, Italy
E-mail: G.cecilia86@yahoo.it

Abstract

We report on a 19-months-old girl, with early onset afebrile seizures and mild developmental delay. She presented with afebrile generalized tonic-clonic seizures, after the first vaccination (Hexavalent vaccination, 5 months-old). She was referred to a child neurologist and treated with phenobarbital. The patients underwent neurological follow-up from 5 to 18 months of age. Seizures were not controlled and mild developmental delay was evident. At the age of 19 months, she presented with convulsive status epilepticus and treated with 35 mg of endorectal diazepam before admission, with subsequent cardiorespiratory failure. She was admitted to the intensive care unit of our hospital. Interictal awake electroencephalogram (EEG) showed: activity of continuous di used theta waves with sporadic Frontal focal spikes. After 13 days in intensive care unit the patient was moved to our child neurology ward, where she presented in a sleepiness state. EEG showed the presence of independent multifocal sharp waves, mostly frontal, epileptogenic abnormalities. Brain magnetic resonance imaging revealed no significant abnormalities, only mild cerebral atrophy. Due to the persistence of diffuse slowing at the EEG, an immune encephalopathy was suspected and, Dexamethasone and Immunoglobulin therapy was performed, without benefit. When the patient was seizure-free, she was discharged with Phenobarbital and Levetiracetam therapy (started in Intensive care unit). Twenty days later, at the follow-up in our Unit, the infant was significantly improved (after 3 weeks the patient was seizure-free, neurological examination showed marked improvement of gait stability and motor coordination. Next generation sequence analysis showed a heterozygous mutation (c.4423G>A (p.Gly1475 Arg) in the SCN8A gene (Chromosome 12q13). No further seizures occurred for 3 months.
***Conclusion*: This report reviewed the clinical features of a patient with a *de novo* SCN8A mutation. Our data suggest that therapy with Phenobarbital and Levetiracetam could be effective in treating refractory epilepsy in a case with a SCN8A (c.4423G>A (p.Gly1475Arg) mutation.**

KEY WORD: SCN8A, epilepsy, seizures, Chromosome 12q13, EEG, Dravet-like.

Introduction

SCN8A is located on Chromosome 12q13 and encodes the sodium voltage-gated channel alpha subunit (Nav1.6), which functions in the rapid depolarization of sodium channels during generation of action potentials in neurons. It leads to impaired sodium channel inactivation, persistent sodium current and increased neuronal activity. A hyperpolarizing shift in voltage dependence of channel activation was observed, also leading to hyperactivity. This gain-of function mechanism is opposite to the one underlying Dravet syndrome, where loss-of-function mutations in SCN1A are most common (1) (Tab. 1).
Rare *de novo* mutations of sodium channels are thought to be an important cause of sporadic epilepsy. SCN8A encephalopathy was first identified in 2012, and an understanding of the severe impact of SCN8A mutations is just beginning to emerge.
SCN8A pathogenic variants have been associated with developmental delay prior to and/or after onset of seizures, with or without cerebellar ataxia, intellectual disability without seizures and epileptic encephalopathy. Sudden unexpected death in epilepsy (SUDEP) has been reported in approximately 10% of published cases (2, 3).
EEG may be normal or exhibit focal or multifocal epileptiform activity at onset.
The Brain MRI is usually normal at the onset of seizures; however, abnormal findings may include

cerebral atrophy and hypoplasia of the corpus callosum.
Epileptic encephalopathy is characterized by seizure activity that progresses to cerebral dysfunction leading to severe cognitive, motor and behavioral impairments (4). Approximately 1% of early infantile epileptic encephalopathies are associated with missense mutations in the SCN8A gene, and approximately 50 cases have been described in the literature (5-7). In a few cases, the mutation was inherited from a mosaic parent, but the majority of cases are associated to *de novo* missense mutations (4). Individuals present with various types of seizures, including tonic-clonic, generalized tonic, atonic, myoclonic and focal and absence seizures, whereas febrile seizures are rare (8). There is often developmental regression, and movement disorders are present with 50% of affected individuals unable to sit or walk.
In this paper we describe a case of a female patient, 19 months old, with heterozygous mutation of SCN8A gene (c.4423G>A (p.Gly1475Arg) treated with Phenobarbital and Levetiracetam, which had permitted seizure's control for more than 3 months.

Case report

We report on 19-months-old girl, with early onset afebrile seizures. She was born at 41 weeks from uneventful pregnancy. Birth weight was 3000 gr, Apgar score 1': 2, 3': 6; 5': 9, as a complication of nuchal loops around the fetal neck. At the age of 5 months, after Hexavalent vaccination (7 hours late), she had afebrile generalized tonic-clonic seizures and hospitalized. Brain magnetic resonance imaging revealed no significant abnormalities (only mild cerebral atrophy). The EEG showed diffuse slowing. She started therapy with Phenobarbital and underwent neurological follow-up up to the age of 18 months (Tab. 2).
From the age of 5 months to 19 months, the occurrence of drug resistant seizures lead to multiple antiepileptic agents' changes. Topiramate withdrawal was due to several adverse events (loss of appetite, weight loss, flushing, anhidrosis). She presented mild developmental delay mainly involving verbal and posturo-motor skills. After a mild seizures' improvement and the starting of drug switching, for two consecutive days, she presented with clustering seizures, each one treated at home, with endorectal Diazepam up to a total amount of 35 mg (15 mg during the first day, 20 mg during the second day). After 24 hours from the seizures onset the patient was admitted to the hospital where she has had new seizures treated with further Diazepam (not specified the dosage). At this time, the patient presented with cardiorespiratory failure, needed activation of base life support, intubation and transfer to the Intensive care unit of our Hospital. At the admission the patient presented clonic seizures and started Levetiracetam administration.
After 13 days in Intensive Care Unit the patient was moved to our child neurology ward. At the admission, she presented in a drowsiness/sleepiness state, severe hypotonia, spontaneous motility was characterized by unvoluntary stereotyped movements, several

Table 1 - Differences between SCN8A-related epilepsy with encephalopathy and Dravet syndrome (10).

	Dravet syndrome	***SCN8A-related epilepsy***
- Age of onset	<12 months	0-22 months
- Febrile seizures	common	rare
- Infantile spasms	yes	yes (which are not a feature of Dravet syndrome)
- Myoclonic seizures	common	rare
- Hypotonia and movement disorders	not typical	common
- EEG findings	generalized spike wave	variant
- Medications	do worse on sodium channel blockers	sodium channel blockers (carbamazepine, oxcarbazepine, and phenytoin)

Table 2 - Therapeutic follow-up.

Patient Age	***Drugs***
from 5 months to 9 months	Phenobarbital
from 9 months to 12 months	Valproate and Phenobarbital
from 12 months to 16 months	Topiramate and Phenobarbital
from 16 months to 19 months	only Topiramate

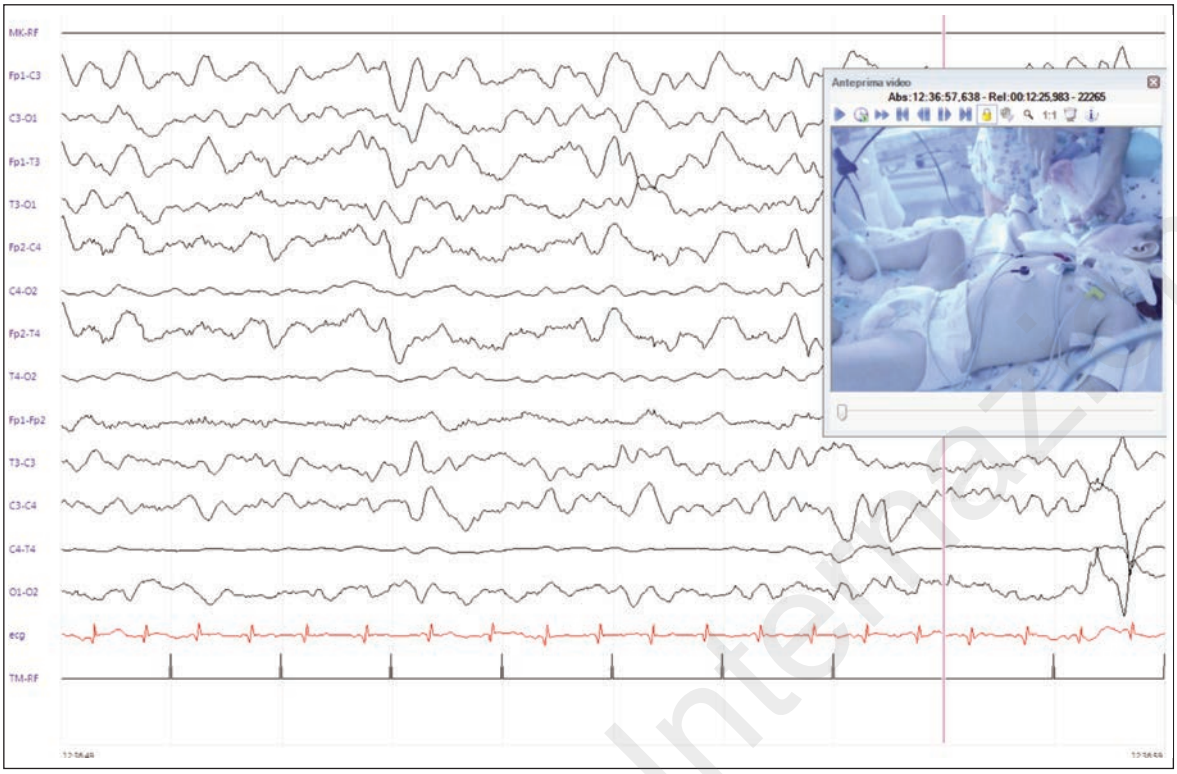

Figure 1 - Video-EEG monitoring of the patient during the admission in Intensive care unit where she was treated with Levetiracetam. Interictal awake electroencephalogram (EEG) showed: activity of continuous diffused theta waves with sporadic Frontal focal spikes. During this registration the patient has presented stereotyped automatism.

investigations have been performed: EEG, MRI, visual evocked potentials, lumbar puncture, all unrevealing. SPETTRO-RMN (which showed delayed myelination and mild cerebral atrophy) and low-positivity of Ab anti GAD=4). Due to the above mentioned neurological status and the persistency of diffuse slowing at the eeg, an immune encephalopathy was hypothesized. Dexamethasone (2 mg four times a day) Immunoglobulin therapy (4 gr/die, for 5 days) were administered without benefits. At the hospital discharge, the patient was undertreated with Phenobarbital (started in our Unit) and Levetiracetam. At the follow-up (twenty days later) she didn't present further seizures. However, psychomotor status was unchanged. The infant was significantly improved: she started to speak, to walk with support and a re-started good interaction with people. During the follow-up EEG showed the presence of independent multifocal sharp waves, mostly frontal, epileptogenic abnormalities. After 1 month and half the improvement described increased. The patient was admitted for a control and we received the results of NGS that showed *de novo* SCN8A mutation (c.4423G>A (p.Gly1475Arg). She continued treatment with Phenobarbital and Levetiracetam, which has permitted seizure's control for more than 3 months (Tab. 3).

Discussion

Here we reported on a 19-months-old girl with a *de novo* SCN8A mutation and suggested the initial efficacy of combination therapy of Phenobarbital and Levetiracetam for refractory epilepsy in this patient. No clear genotype-phenotype correlation emerged between SCN8A pathogenic variant and seizures' onset, seizures' type and neurodevelopmental impairment. Most pathogenic variants are located in the transmembrane segments of the channel. Penetrance for SCN8A-related epilepsy with encephalopathy is unknown but assumed to be complete.

To date, no clear guidelines for treatment of patients with SCN8A-related epilepsy have been provided. However, vigorous attempts to control seizures are warranted because of an increased risk for sudden unexplained death in such patients (SUDEP).

Several studies showed as patients with SCN8A-related epilepsy with encephalopathy favorably respond to the class of antiepileptic drugs (AEDs) that block sodium channels such as Phenytoin, Valproate, Carbamazepine, Lacosamide, Lamotrigine, Rufinamide and Oxcarbazepine. Treatment with Corticosteroids, Immunoglobulins, Vagus nerve stimulator, Ketogenic diet, Cannabinoids has been attempted in drug-resistant patients.

Table 3 - SCN8A Studies in literature. References.

References	Cases	Development	Seizure types	RMN	EEG	Variants SCN8A
Larsen J, et al.[I]	17 patients	-Regression development -Intellectual disability (mild /severe) -Hypotonia, dystonia, hyperreflexia, and ataxia	-Focal, tonic, clonic, myoclonic, absence seizures, and epileptic spasms -Refractory to antiepileptic therapy -Not triggered by fever	- The abnormal findings included cerebral atrophy and hypoplasia of the corpus callosum	Moderate to severe background slowing with focal or multifocal epileptiform discharges	De novo: - Arg1617Gln - Val960Asp - Gln1801Glu - Arg1872Gln - Ala890Thr - Ile1479Val - Arg1872Trp - Phe260Ser - Ile1605Arg - Val410Leu Pro1428_Lys1473del - Ala1650Thr - Asn215Arg - Val1592Leu - Inherited, somatic 13% mosaic: Leu1331Valb
Ohba C, et al.[II]	7 patients	-Delay or regression in development -Severe intellectual disability	-Generalized tonic-clonic, atypical absence, partial, apneic attack, febrile convulsion, and loss of tone and consciousness -Initially uncontrollable seizures by any drugs	-Cerebellar and cerebral atrophy in one and six	- Normal or diffuse or unilateral hemispheric irregular polyspike-and-slow wave complexes	- p.Asn1466Lys - p.Val216Asp - p.Phe846Ser - p.Arg1617Gln - p.Asn1466Thr - p.Arg1872Trp - p.Ala1650Thr
Kong W, et al. [III]	5 patients	-Moderate to severe development disability -Intellectual disability	Generalized or Focal and secondary generalized tonic–clonic seizures, spasms, myoclonus	Normal	-Normal or- Diffuse/ unilateral Spike and spike-wave complexes	p.Ala890Thr p.Leu407Phe p.Arg850Gln p.Ser1596Cys p.Arg1617Gln
Morgan LA, et al.[IV]	17 patients	-Development regression -Intellectual disability -Hypotonia, dystonia, hyperreflexia, choreoathetosis, and ataxia. Two patients died early in childhood	-Focal clonic seizures evolving to bilateral convulsions, tonic seizures, epileptic spasms, and myoclonic seizures -Status epilepticus (n=8) -Refractory epilepsy	Cerebral atrophy and hypoplasia of the corpus callosum, or not available (n=4)	Normal focal or multifocal epileptiform activity	

To be continued

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Berghuis B, et al. [V]	One patient	-Intellectual disability -Attention problems periods of aggressiveness	Absence seizures		-Theta/delta activity. Bilateral synchronous generalized high voltage (poly) spike slow wave discharges with a frequency of 2-3/s	- p.I1583T - p.S524Y
Vaher U, et al.[VI]	One patient	-Movement disorders -Multiple congenital anomalies -Death at the age of 17 months because of respiratory illness				c.3979A>G p.Ile1327Val
de Kovel CG, et al. [VII]	One patient	-Severe psychomotor retardation -Developmental regression	Convulsive seizures and SUDEP	Diffuse brain atrophy including slight atrophy of the cerebellum, and interruption of myelination	Hypsarhythmia multifocal epileptiform discharges and background slowing	p.Arg233Gly
Takahashi S, et al. [VIII]	One patient	Severe development disability	Generalized tonic seizures and focal motor seizures	Focal epileptic activity (4 moths) Multifocal spikes (>4moths)	Demonstrated brain atrophy, which appeared to progress with seizure aggravation	c.5614C>T p.Arg1872Trp
Blanchard MG et al. [IX]	3 patients	Intellectual disabilities	None or absences and tonic-clonic seizures		Cerebral atrophy	c.2952C>G p.(Asn-984Lys) near D2S6 c.4351G>A p.(Gly-1451Ser) in D3S6 c.172G>A p.[Asp58Asn]
Estacion M, et al. [X]	One patient	Developmental delay, progressive loss of neurological function, intellectual disability -hypotonia, spasticity	Myoclonic jerks and stiffness in the neonatal period Hyperekplexia intractable epilepsy	Multifocal epileptiform activity with a normal background	Delayed myelination	p.Thr767Ile
Anand G et al. [XI]	2 patients (father and son)	Normal	Focal seizures with secondary tonic generalization generalized tonic-clonic seizures	Normal	Background rhythm slow and disorganised for age	c.5630A > G p.[Asn1768Asp]

To be continued

Continue from **Table 3**

Veeramah KR, et al. [XII]	One patient	-Autism, intellectual disability -Ataxia, hypotonia and difficulties with coordination and balance	Refractory epilepsy, generalized seizures. Epilectic spasms sudden unexplained death in epilepsy	Normal	Bifrontal spikes and brief bursts of fronto-centrally predominant generalized spike-wave activity	c.5302A>G [p.Asn1768Asp]
Malcolmson J, et al. [XIII]	One patient	-Global developmental delay -Hypotonia	Generalized tonic-clonic seizures on awakening	An incidental germinolytic cyst, unrelated to the proband's clinical presentation	Multifocal sharp waves	p.Leu267Ser
Singh R, et al.[XIV]	One patient	Severe developmental delay	Stereotyped tonic/ tonic-clonic seizures progressing to epileptic status	Mild cerebellar volume loss with age-appropriate myelination	Generalized spike and wave discharges	p.Ile1327Val
Fung LW, et al.[XV]	One patient	Moderate intellectual disability, ataxia, hypotonia and dysarthria	Generalized tonic-clonic seizure, myoclonus, atypical absences, focal clonic seizures		Diffuse slow delta waves frontal spike and slow-wave discharges	c.T4862G: p.Leu1621Trp
McNally MA, et al. [XVI]	One patient	Axial hypotonia	Clinical prenatal-onset seizures Generalized tonic seizures	Hyperintense signal within the superior cerebellar peduncles in the dorsal mesencephalon	Waveforms between hemispheres	p.Ile240Val
Wagnon JL, et al.[XVII]	3 patients	Moderate/severe Intellectual disability	Generalized tonic-clonic	Cerebella and cerebral atrophy Bilateral flat insular cortex	Generalized slowing, severe diffuse encephalopathy	p.Arg1872Gln
Gardella E, et al.[XVIII]	16 patients	All individuals except 1 had normal cognitive and motor milestones	Afebrile focal or generalized tonic-clonic seizures during the first to second year of life		Focal or generalized spike-wave	c.4447G>A; p.E1483K
Trudeau MM, et al.[XIX]	One patient	-Mental retardation -Tremor and ataxia		Pancerebellar atrophy		Pro1719ArgfsX6
Wang J , et al. [XX]	6 patients	-Mild or severe psychomotor retardation	Focal seizures Febrile/afebrile convulsion	Normal	Hypsarrhythmia, burst-supperession	p.Val1598Ala
Wagnon JL et al.[XXI]	2 patients	-Intellectual disability -Developmental delay	No seizures	Normal	Normal	p.Gly964Arg in D2S6 p.Glu1218Lys in D3S1

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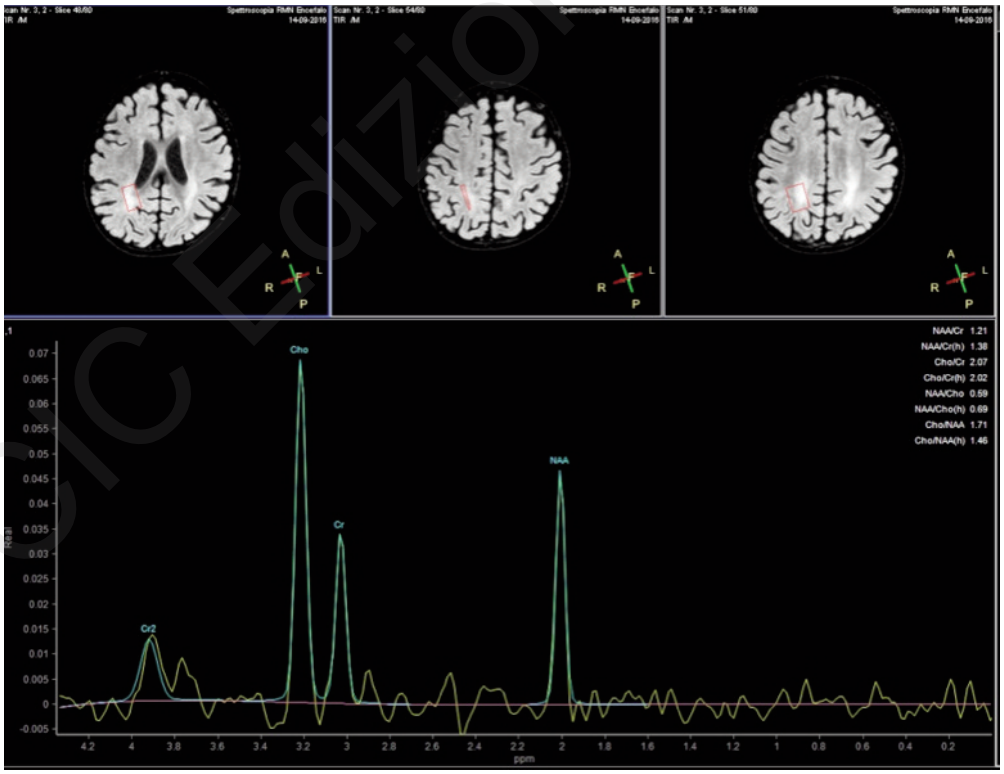

Figure 2 - SPECT-MRI: Brain magnetic resonance imaging (MRI) conducted during admission in our Unit after 20 days old Dexamethasone treatment. It showed delayed myelination and mild cerebral atrophy (may be caused by the corticosteroid therapy).

Our patient has been initially treated with valproate, but without benefits. Thereafter, only a combination of Phenobarbital and Topiramate was transiently effective, in the second time Dexamethasone and after combination of Phenobarbital and Levetiracetam (Levetiracetam is a second-generation antiepileptic drug (AED) with a unique mechanism of action that involves interactions with the synaptic vesicle protein) (9). The latter combination induced disappearance of the seizures for 3 months, while neurodevelopment of the patient improved. As opposed to our paper, other Author showed as Levetiracetam was ineffective or occasionally associated with an increase in seizure frequency in several pedigrees (10).

In conclusion, SCN8A encephalopathy is a relatively new clinical syndrome that needs to be genotypically and phenotypically defined, yet. Our case report is aimed to contribute to the development of strategies for clinical management, drug selection and individualized patient care (11).

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